WHAT IS CLAIMED

1. A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse lacking functional T and B cells and having a genome which comprises a urokinase-type plasminogen activator (uPA) gene, expression of said uPA gene resulting in liver degeneration;

b. repopulating the parenchyma of the degenerated liver by transplanting xenogenic mammalian hepatocytes that are a natural host for infection with one or more compatible hepatitis virus into said liver; and

c. infecting the xenogenic mammalian hepatocytes with said one or more compatible hepatitis virus,

thereby making said chimeric mouse.

2. The method of claim 1 wherein said uPA gene encodes secreted uPA.

3. The method of claim 1, which comprises infecting the xenogenic mammalian hepatocytes with hepatitis virus prior to said transplanting.

4. The method of claim 1, which comprises infecting the xenogenic mammalian hepatocytes with hepatitis virus following said repopulation.

5. The method of claim 1, wherein the xenogenic mammalian hepatocytes are selected from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

6. The method of claim 1, wherein the compatible mammalian hepatitis virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus,

hepatitis F virus or hepadnavirus.

7. The method of claim 1, wherein the immunetolerant mouse which has a degenerated liver is created by:

a. crossing a hemizygous or homozygous urokinase-type plasminogen activator (uPA) transgenic mouse with a homozygous Recombination Activation Gene 2 (RAG-2) knockout mouse to generate F1 uPA hemizygous, RAG-2 hemizygous sibling mice; and

b. crossing the F1 mouse to another sibling F1 mouse or to a RAG2 homozygous mouse to generate a uPA hemizygous or homozygous, RAG2 homozygous (uPA/RAG2) F2 mouse.

8. The method of claim 6, wherein the xenogenic mammalian hepatocytes are from a human and the compatible mammalian hepatitis virus is human hepatitis C virus.

9. A chimeric mouse model system for hepatitis comprising:

an immunetolerant mouse lacking functional T and B cells,

said immunetolerant mouse having a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant mouse, and said degenerated liver being repopulated with transplanted xenogenic mammalian hepatocytes that are infected with at least one compatible mammalian hepatitis virus.

10. The chimeric mouse model system of claim 9, wherein the xenogenic mammalian hepatocytes are infected with hepatitis virus prior to said transplantation.

11. The chimeric mouse model system of claim 9, wherein the xenogenic mammalian hepatocytes are infected with

hepatitis virus following said repopulation.

12. The chimeric mouse model system of claim 9 wherein said uPA gene encodes secreted uPA.

13. The chimeric mouse model system of claim 9, wherein the xenogenic mammalian hepatocytes are selected from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

14. The chimeric mouse model system of claim 9, wherein the compatible mammalian hepatitis virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

15. The chimeric mouse model system of claim 9, wherein the immunetolerant mouse having degenerated liver parenchyma is hemizygous or homozygous for said urokinase-type plasminogen activator (uPA) gene and is homozygous for a Recombination Activation Gene 2 (RAG-2) knockout mutation.

16. The chimeric mouse model system of claim 14, wherein the source of the xenogenic mammalian hepatocytes is a human and the compatible mammalian hepatitis virus is human hepatitis C virus.

17. A method for screening a test compound for anti-viral activity, comprising:

a. administering said test compound to an immunetolerant chimeric mouse lacking functional T and B cells which has a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant chimeric mouse, said degenerated liver being repopulated with transplanted xenogenic mammalian hepatocytes that are infected with at

least one compatible mammalian hepatitis virus; and

b. assaying the level of replication of the virus,

thereby screening said test compound for anti-viral activity.

18. The method of claim 17 wherein said uPA gene encodes secreted uPA.

19. The method of claim 17, which comprises comparing the level of viral replication in said mouse and in a control mouse which has not been administered the test compound.

20. The method of claim 17, wherein the xenogenic mammalian hepatocytes were infected with the compatible mammalian hepatitis virus prior to said transplanting.

21. The method of claim 17, wherein the xenogenic mammalian hepatocytes were infected with the compatible mammalian hepatitis virus following said repopulation.

22. The method of claim 17, which comprises selecting the xenogenic mammalian hepatocytes from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrel, and woodchuck hepatocytes.

23. The method of claim 17, wherein the compatible mammalian hepatitis virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

24. The method of claim 23, wherein the compatible mammalian hepatitis virus is hepatitis C virus.

25. The method of claim 17, wherein the immunetolerant mouse which has a degenerated liver is hemizygous or homozygous for said urokinase-type plasminogen activator (uPA) gene and homozygous for a Recombination Activation Gene 2 (RAG-2) knockout mutation.

26. The method of claim 17, wherein the antiviral compound is a member selected from the group consisting of interferons, cytokines, interleukins, growth factors, hormones, nucleoside analogues, and antisense DNA/RNA.

27. A method for screening a test compound for anti-cancer activity, comprising:

a. administering said test compound to immunetolerant chimeric mice lacking functional T and B cells,

said mice having a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant chimeric mice, and

said degenerated liver parenchyma being repopulated with transplanted xenogenic mammalian hepatocytes that are infected with at least one compatible mammalian hepatitis virus capable of causing hepatocellular carcinoma in said xenogenic hepatocytes; and

b. assaying said mice for the development of hepatocellular carcinoma virus,

thereby screening said test compound for anti-cancer activity.

28. The method of claim 27 wherein said uPA gene encodes secreted uPA.

29. The method of claim 27, which comprises comparing the presence of unique viral DNA integrations in the liver of said mouse and in a control mouse which has not been administered the test compound.

30. The method of claim 27, wherein the chimeric mouse has precancerous or malignant cancerous hepatic tissue and wherein the development of hepatocellular carcinomas is assayed by monitoring for the prevention of the development of cancerous tissue from precancerous tissue or the amelioration of the malignant cancerous tissue.

31. The method of claim 27, which comprises comparing the assay in the chimeric mouse with the same assay carried out in a control mouse which has not been administered the test compound.

32. The method of claim 27, wherein the xenogenic mammalian hepatocytes were infected with hepatitis virus prior to said transplantation.

33. The method of claim 27, wherein the xenogenic mammalian hepatocytes were infected with hepatitis virus following said repopulating.

34. The method of claim 27, wherein the xenogenic mammalian hepatocytes are selected from the group consisting of human, chimpanzee, baboon, wooly monkey, ground squirrels and woodchuck hepatocytes.

35. The method of claim 27, wherein the compatible mammalian hepatitis virus is at least one of a compatible mammalian hepatitis A virus, hepatitis C virus, hepatitis D virus coinfected with hepadnavirus, hepatitis E virus, hepatitis F virus or hepadnavirus.

36. The method of claim 27, wherein the immunetolerant mouse which has a degenerated liver is hemizygous or homozygous for said urokinase-type plasminogen activator (uPA) gene and homozygous for a Recombination Activation Gene 2 (RAG-2) knockout mutation.

37. The method of claim 35, wherein the source of the xenogenic mammalian hepatocytes is a human and the compatible mammalian hepatitis virus is human hepatitis C virus.

38. The method of claim 27, wherein the anticancer compound is a member selected from the group consisting of interferons, cytokines, interleukins, growth factors, hormones, nucleoside analogues, and antisense DNA/RNA.

39. A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse, said immunetolerant mouse having a degenerated liver due to expression of a urokinase-type plasminogen activator (uPA) gene and lacking functional T and B cells, said uPA gene being present in the genome of said immunetolerant mouse;

b. transplanting human hepatocytes having at least 80% viability by intrasplenic injection to repopulate the parenchyma of the degenerated liver; and

c. infecting said hepatocytes with one or more compatible hepatitis virus,

thereby making said chimeric mouse.

40. The method of claim 39 wherein said immunetolerant mouse is about 10-14 days old at the time of transplanting said human hepatocytes.

41. The method of claim 40 wherein the transplanted human hepatocytes reconstitute approximately 10% of the degenerated liver.

42. The method of claim 39 wherein said uPA gene encodes secreted uPA.

43. The method of claim 39, which comprises

infecting said hepatocytes with hepatitis virus prior to said transplanting.

44. The method of claim 39, which comprises infecting said hepatocytes with hepatitis virus following said repopulation.

45. The method of claim 39, which comprises infecting said hepatocytes with hepatitis C virus.

46. A method of making a chimeric mouse, comprising:

a. creating an immunetolerant mouse lacking functional T and B cells and having a genome which comprises a urokinase-type plasminogen activator (uPA) gene, expression of said uPA gene resulting in liver degeneration;

b. repopulating the parenchyma of the degenerated liver by transplanting human hepatocytes into said liver; and

c. infecting the xenogenic mammalian hepatocytes with human hepatitis C virus,

thereby making said chimeric mouse.

47. A chimeric mouse model system for hepatitis comprising:

an immunetolerant mouse lacking functional T and B cells,

said immunetolerant mouse having a degenerated liver parenchyma due to expression of a urokinase-type plasminogen activator (uPA) gene present in the genome of said immunetolerant mouse, and said degenerated liver being repopulated with transplanted human hepatocytes that are infected with human hepatitis C virus.